

REVIEW

Oncostatin M: an interleukin-6-like cytokine relevant to airway remodelling and the pathogenesis of asthma

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Introduction

Asthma affects approximately 5% of the adult population in the western world and is increasing dramatically in developing countries [1]. In Australia alone, it presents an annual cost burden to the community of AU\$585–\$720 million [2]. The major characteristics of asthma include airflow obstruction, bronchial hyper-responsiveness (BHR) and airway inflammation [3]. While asthma is generally a reversible condition, it is apparent that some people with chronic disease develop irreversible structural changes in their airways from abnormal repair and remodelling processes [4].

Oncostatin M (OSM) is a member of the IL-6 family of cytokines. These cytokines are grouped together on the basis of shared structural and functional characteristics and the shared usage of the signal transducing sub-unit, gp130. Despite numerous reports implicating OSM as a key modulator of chronic inflammatory diseases, there have been limited studies implicating the role of this cytokine in lung disease and, in particular, asthma. This review aims to provide evidence to suggest that OSM may play an important role in the development of airway wall remodelling and, as a consequence, may be a suitable target for further research in the pathogenesis of asthma and its treatment.

Asthma

Asthma is a complex chronic inflammatory disease of the airways [5]. Despite significant advances in our knowledge of the disease, the mechanisms underlying its pathogenesis remain unclear. It has been widely assumed that airway hyper-responsiveness and pathology are reversible, either spontaneously or via treatment. However, it is increasingly apparent that irreversible structural changes of the airways can develop. These structural changes, collectively referred to as airway remodelling, play an important role in generating the manifestations of asthma [6]. It is presumed that airway remodelling contributes to the sub-optimal responses to corticosteroids and the persistent BHR and progressive lung function decline that occurs in asthmatic individuals with

severe or chronic disease [7]. Evidence of remodelling in asthmatic airways includes epithelial derangement, thickening of the sub-epithelial basal lamina, an increased number of fibroblasts, and an altered deposition and composition of the extracellular matrix (ECM) [8]. It is likely that airway remodelling is a consequence of an aberrant injury/repair response driven by the inflammatory process. Molecules that modulate the injury/repair response, therefore, are good candidates for therapeutic targets.

OSM

OSM is a multi-functional cytokine belonging to the IL-6 family of cytokines. These cytokines are grouped together on the basis of their shared structural and functional similarities and the shared use of the signal transducing sub-unit, gp130. Other members of this family include leukaemia inhibitory factor (LIF), IL-6, IL-11, ciliary neurotrophic factor (CNTF) and cardiotrophin-1 (CT-1). More recently, an additional member to the IL-6 family of cytokines was identified, namely 'novel neurotrophin-1/ B cell-stimulating factor-3' (NNT-1/BSF-3), which has also been referred to as 'cardiotrophin-like cytokine' (CLC) [9–11].

The IL-6 family of cytokines initiates intracellular signalling by forming a homo/heterodimer with the signal transducing sub-unit, gp130, and their specific receptor sub-units (Fig. 1). The signalling pathway for this family of cytokines has been the subject of extensive research (reviewed in [11]). As the receptors for this family of cytokines lack intrinsic tyrosine kinase activity, signal transduction is mediated through the recruitment and activation of multiple members of the janus kinase (JAK) family, including JAK-1, JAK-2 and TYK-2. Juxtapositioning of the cytoplasmic JAKs to the receptors results in the phosphorylation of highly conserved tyrosine residues in gp130, LIFR β and OSMR β . The phosphorylated tyrosine residues on the receptor chains create docking sites for the SH2 domain containing intermediate-signalling molecules, which include signal transducers and activators of transcription (STATs) and the cytoplasmic tyrosine phosphatases: Shc and SHP-2. The STATs, for instance, after binding to the receptor, autophosphorylate and form either homo- or heterodimers that translocate to the nucleus, where they bind DNA and regulate transcription of target genes, such as the acute-phase response genes [12]. In contrast, after binding to the receptor,

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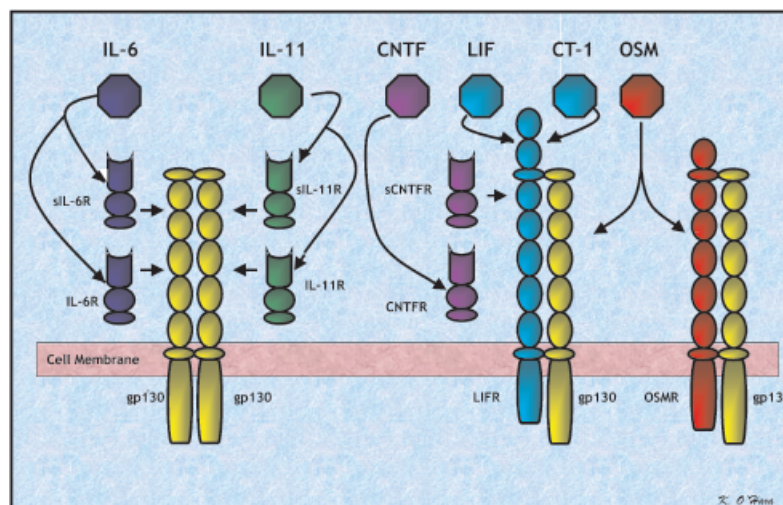


Fig. 1. IL-6 family cytokines and their receptor complexes.

phosphorylation of SHP-2 creates a docking site for Grb2/SOS. Recruitment of the Grb2/SOS complex leads to the activation of the Ras-Raf-MAP kinase (MAPK) pathway [13]. Similarly, the tyrosine phosphatase Shc is also able to recruit the Grb2/SOS complex and activate the MAPK pathway [14]. Murine gene-targeting strategies have been used to introduce mutations into the individual signalling 'modules' of gp130, allowing dissection of the individual contribution of the gp130-mediated JAK/STAT pathway from that transduced by the MAPK pathway. These studies reveal tight reciprocal negative regulation between JAK/STAT and MAPK pathways, suggesting that balanced signalling from each pathway is critical for the physiological responses to the IL-6 family cytokines [15, 16]. The simultaneous activation of these gp130-mediated pathways can, therefore, produce disparate effects on cells, including growth arrest and differentiation or proliferation (reviewed in [11]).

Of the IL-6 cytokines, OSM is most closely related to LIF. Indeed, OSM and LIF are located immediately adjacent to each other on chromosome 22 and, as such, it is thought that these cytokines are derived from the same ancestral gene [17]. Furthermore, both OSM and LIF are able to signal through the same receptor complex, composed of LIFR β and gp130, which may in part explain the overlapping activities of these cytokines. OSM, however, is also able to signal through its own unique receptor complex composed of gp130 and the OSMR sub-unit (Fig. 2) [18]. These two receptor complexes are coupled to distinct signal transduction pathways [13]. Where both receptors are present, OSM appears to preferentially signal through the OSMR/gp130 complex [19].

OSM in the pathogenesis of asthma

There are a number of activities displayed by the IL-6 family of cytokines, which suggest that they are important in modulating inflammation and, therefore, may play a role in the pathogenesis of asthma. For instance, members of this cytokine family are produced in the airway in response to inflammatory stimuli, are able to induce an acute-phase

response, inhibit pro-inflammatory mediators and have been shown to have pro-fibrotic properties [20–23]. Despite increasing evidence to suggest that this family of cytokines plays an important role in asthma, their distinct role in this complex disease is still unclear.

Due to its pleiotropic nature, there is a vast array of biological activities exhibited by OSM. The role of OSM in cancer, haematopoiesis, cholesterol metabolism and atherosclerosis has been well documented [24–26]. OSM has also been identified as an important cytokine in inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis [27, 28]. In addition, Wallace and Brown [29] have a US patent for using OSM as a method for inhibiting gastrointestinal inflammation, rheumatoid arthritis and multiple sclerosis. Although the biological activities displayed by OSM are vast, this review will focus on its role as a modulator of inflammation in the lung. In particular, OSM seems to have potent pro-fibrotic, anti-inflammatory and antiproteolytic activities and, as such, may be a key mediator of the wound repair response following injury.

OSM is produced in cell types that are up-regulated in asthma

OSM is produced in cell types that are known to increase in number and activity in asthma, including monocytes and macrophages, activated T cells and neutrophils [17, 30, 31]. More recently, it has also been demonstrated that OSM is produced by dendritic cells [32]. In contrast to other members of this family, there is no evidence to suggest that OSM is produced in resident cells, such as epithelial cells, fibroblasts or airway smooth muscle [19]. In the lungs, therefore, it seems that OSM is primarily produced by infiltrating cells in response to injury.

OSM is antiproteolytic in the lungs

A balance between the synthesis and degradation of the ECM is required for tissue homeostasis. A key component in

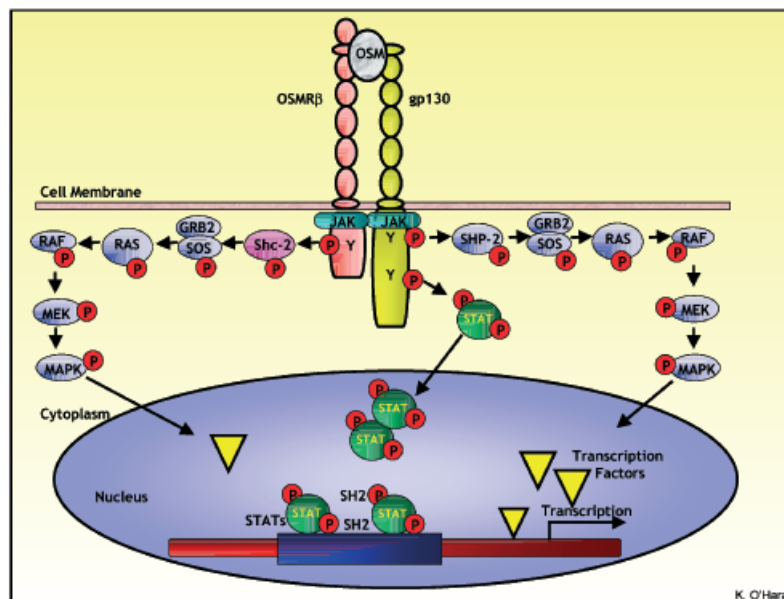


Fig. 2. Oncostatin M (OSM) signal transduction through the OSMR β / gp130-specific receptor complex. After ligand binding, juxtapositioning of the cytoplasmic JAKs leads to the phosphorylation of highly conserved tyrosine residues (Y) in gp130 and OSMR β . The phosphorylated tyrosine residues on the receptor chains create docking sites for the SH2 domain containing intermediate-signalling molecules, which include signal transducers and activators of transcription (STATs) and the cytoplasmic tyrosine phosphatases: Shc and SHP-2. The STATs, for instance, after binding to the receptor, autophosphorylate and form either homo- or heterodimers that translocate to the nucleus, where they bind DNA and regulate transcription of target genes, such as the acute-phase response genes. In contrast, after binding to the receptor, phosphorylation of SHP-2 creates a docking site for Grb2/SOS. Recruitment of the Grb2/SOS complex leads to the activation of the Ras-Raf-MAP kinase (MAPK) pathway. Similarly, the tyrosine phosphatase Shc is also able to recruit the Grb2/SOS complex and activate the MAPK pathway. OSMR β sub-unit specifically recruits Shc, whereas LIFR β and gp130 utilize SHP-2, to activate the MAPK pathway.

regulating homeostasis is the interaction of the degradative proteases and their specific inhibitors, antiproteases. OSM is a potent inducer of specific antiproteases, including α 1-antitrypsin and α 1-proteinase inhibitor from human lung-derived epithelial cells [33, 34]. OSM has also been shown to be a potent inducer of the acute phase proteins, serum amyloid A and α 1-glycoprotein from hepatocytes as well as at the site of injury [35]. Furthermore, OSM up-regulates the production of IL-6, a potent inducer of the acute-phase response, in human endothelial cells [36].

Excess ECM deposition in the airway wall is at least partly responsible for the characteristic feature of airway remodelling that occurs in asthmatic patients. Airway inflammation after an asthmatic exacerbation correlates with the overproduction of matrix metalloproteinases (MMPs), in particular MMP-9 and MMP-2 [37]. Under normal conditions, MMPs are inhibited by specific tissue inhibitors of metalloproteinases (TIMP). OSM is a potent inducer of TIMP-1 expression in human lung fibroblasts and synovial fibroblasts *in vitro* [38]. In contrast to the lung, OSM is a potent inducer of MMP-1, MMP-8, MMP-13 and MMP-14 in human chondrocytes [39]. Hence, the effect of OSM on protease/antiprotease balance appears to vary between different tissues.

OSM is pro-fibrotic in the lungs

A growing number of reports have demonstrated that OSM displays pro-fibrotic activities in various tissue/disease mod-

els. For instance, OSM has been found to stimulate the growth of mouse synovial fibroblasts and the growth of human dermal fibroblasts *in vitro* [40, 41]. OSM also promotes the production of collagen and glycosaminoglycan in dermal fibroblasts [42]. In addition, Bamber et al. [43] found that transgenic mice that over-expressed bovine OSM in the pancreas displayed extensive fibrosis, characterized by excessive collagen deposition [43]. In contrast to its anabolic properties in these cell types, OSM seems to have a catabolic effect in chondrocytes causing increased collagen degradation, a characteristic feature of bone degenerative diseases such as arthritis [44].

Extensive fibrosis is not a prominent feature in asthma, but nonetheless it is an important characteristic of its pathology [45]. In fact, it is likely that the development of fixed airway obstruction in asthma is at least, in part, due to airway fibrosis [6]. Indeed, deposition of collagen in the sub-epithelial basement membrane is a characteristic feature of the remodelling response in asthma [46]. It is well established that fibroblasts are the major producers of collagen. We have recently shown that OSM stimulates the proliferation and induces collagen production by human lung fibroblasts [19]. Interestingly, as part of their work investigating the molecular mechanism of fibrosis, Ihn et al. [47] identified a dual-function response element that mediates the basal activity and OSM stimulation of the human α 2 collagen promoter in human fibroblasts. More recently, over-expression of OSM in the lungs of mice resulted in increased fibrosis in the ECM, characterized by increased collagen production in the lung parenchyma in areas within or peripheral to the inflammation [48].

OSM is predominantly an anti-inflammatory mediator in the lung

There have been a number of conflicting reports suggesting that OSM is either a pro-inflammatory or anti-inflammatory mediator. Discrepancies may be related to the cell types studied, disease types and severity and different experimental design. In the lungs, however, it seems that OSM may play an important role in the wound repair response after injury.

For instance, OSM is a potent inhibitor of TNF- α release following lipopolysaccharide (LPS) treatment *in vivo* [28]. Although OSM does not inhibit IL-1 directly, it has been found to inhibit IL-1-induced expression of IL-8 and granulocyte-macrophage colony-stimulating factor by synovial and lung fibroblasts *in vitro* [49]. OSM also acts synergistically with IL-1 to induce COX-2 expression and prostaglandin E₂ (PGE₂) release in human airway smooth muscle cells [50]. Furthermore, studies in our laboratory demonstrate that OSM is an important co-factor in the release of PGE₂ and nitric oxide (NO) from lung epithelial cells and may play a role in defence against exogenous proteases such as those derived from house dust mites [51].

Over-expression of OSM in the lungs of Balb/C mice resulted in a vigorous inflammatory response, characterized by increased neutrophil and lymphocyte numbers and a marked increase in collagen deposition [48]. Interestingly, this response was not observed until day 7 after administration of OSM. Others have also shown that OSM is produced late in the cytokine response to injury, suggesting that OSM is an important modulator of the wound repair response, rather than the immediate inflammatory response, following injury [28]. More recently, it has been demonstrated that over-expression of murine OSM in the lungs of pro-allergic C57BL/6 mice induced eotaxin release from fibroblasts and eosinophilic inflammation [52]. Differences in inflammatory cell infiltrate are probably due to the different mouse strains.

Modur et al. [53] found that OSM, when expressed in bacteria, is pro-inflammatory, inducing the expression of adhesion molecules, such as P-selectin and E-selectin, on human umbilical vein endothelial cells (HUVEC) *in vitro* and inducing inflammatory infiltrate *in vivo*. Additionally, OSM has been shown to induce a prolonged increase in P-selectin mRNA and protein in these same cells [54].

In contrast, others have studied the effects of OSM on endothelial cells using highly purified mammalian protein or yeast-derived protein (reviewed in [28]). These *in vitro* and *in vivo* studies did not support Modur's findings. To date, no studies have reported the effect of OSM on the expression of adhesion molecules in human lung tissue.

OSM is not immunosuppressive

Inflammation and the immune response are two immunoregulatory pathways that are often interdependent and therefore difficult to distinguish. However, using murine models of rheumatoid arthritis and multiple sclerosis, Wahl and Wallace [55] were able to distinguish between the inflammatory and immune response. In these studies, they found that treatment with OSM at levels sufficient to inhibit inflamma-

tory/degradative aspects of the disease did not suppress normal antibody production or T cell responsiveness, suggesting that OSM displays anti-inflammatory activities without concordant immunosuppression. In support of OSM's poietic effects on the immune response, transgenic mice over-expressing OSM in the pancreas have been found to display extensive lymphocyte infiltration [43]. Furthermore, over-expression of OSM to the lungs in transgenic mice resulted in dense infiltration of lymphocytes in the peribronchial and perivascular regions and alveolar spaces [48]. Thus, the data available suggest that, in the lungs, OSM is anti-inflammatory and promotes the immune response.

OSM activity varies between different cell types, disease types and severity

Based on these earlier findings, it is likely that different types of inflammation may have differential effects on the expression/activity of OSM β R in the airways. The specific inflammatory response following activation of OSM will be influenced by the tissue distribution of OSM β R, coupled with a specific set of OSM inducible genes [28]. We have recently demonstrated that OSM β R is differentially expressed in cells of the airways from patients with severe asthma or smoking-related chronic obstructive pulmonary disease (COPD) (Fig. 3) [56]. In the airways of fatal asthmatics, for instance, expression of OSM β R was greatest in airway smooth muscle, epithelium, basement membrane and sub-mucosal glands, with very low expression in the vasculature [56]. In contrast, in the airways of patients with severe COPD, expression of OSM β R was greatest in the blood vessels with virtually no expression detected on the airway smooth muscle or sub-mucosal glands.

Genetics of OSM and its receptor component, OSM β R and gp130

In an attempt to further understand the molecular basis of asthma, we have undertaken studies to characterize the genes for OSM and its specific receptor components, gp130 and OSM β R. The gene encoding OSM has been mapped to chromosome 22, while OSM β R and gp130 have both been mapped to chromosome 5. Of note, gp130 has been mapped to chromosome 5q, an area that has already been associated with a number of other candidate asthma genes [1]. The promoter region and complete coding sequence for the genes encoding OSM and gp130 have been cloned and characterized and sequence information is available (Table 1). The complete coding region of the gene encoding OSM β R has also been cloned and characterized, however, the promoter region for this gene has not yet been defined. Consequently, current work in our laboratory is directed towards cloning and characterizing the promoter region of the OSM β R.

Conclusion

There have been a number of studies using OSM as a therapeutic target in various disease states. Wallace and

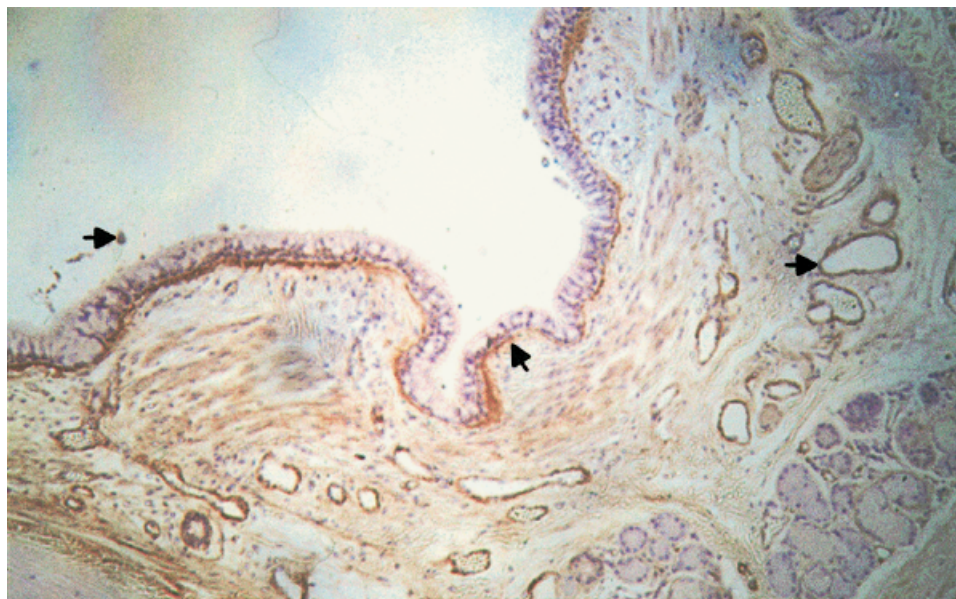


Fig. 3. Immunohistochemical staining of OSMR in formalin-fixed paraffin-embedded section of normal human airways. Expression of OSMR was observed in the epithelium, basement membrane (→), submucosal glands, airway smooth muscle, endothelial cells and lymphomononuclear cells (→). Expression of OSMR was varied in these tissues, depending on the presence and severity of asthma or COPD.

Table 1. Summary of available information for the genes encoding OSM and its receptor components, OSM β R, LIFRB and gp130

	Chromosomal location	Sequence information available	Genbank accession number/reference
Ligand			
OSM	22q12.2	Complete coding sequence Promoter sequence	AF129855 [58] GI189360 [59]
Receptor			
OSM β R	5p15.2	Complete coding sequence + 368 bp 5'UTR Promoter sequence Unknown	HSU60805 [18]
GP130	5q11	Complete coding sequence Promoter sequence	GI186353 [60] U70617 [61]

Brown [29], for example, have reported that administration of OSM was effective in the treatment of gastrointestinal inflammation, rheumatoid arthritis and multiple sclerosis. Furthermore, Richards et al. [57] suggest that OSM is a key component in cellular invasiveness and, as such, have a US patent for using OSM as a method for decreasing metalloproteinase activity, increasing TIMP activity and inhibiting or treating the progression of tumours. They also refer to using OSM as a method for treating inflammatory or degenerative diseases, stimulating erythropoiesis, regulating tissue remodelling and promoting healing after injury [57]. An increased understanding of the genetic basis of complex diseases, combined with current therapies, will allow better targeting of treatments for the individual.

Asthma is a complex chronic inflammatory disease for which there is currently no cure. The evidence presented in

this review suggests that the biological activities of OSM are anti-proteolytic, pro-fibrotic and anti-inflammatory without associated immunosuppression. Thus, it is likely that OSM is an important mediator of the wound repair response following injury which, if unchecked, may lead to remodelling of the airways. Studying the genetic basis of OSM and its specific receptor components in normal and diseased states will, therefore, further increase our understanding of this complex cytokine in the pathophysiology of asthma.

Acknowledgements

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